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(54) **Process for manufacturing
racemic 5-aryl hydantoins and novel
products thereof**

(57) **Process for manufacturing race-
mic 5-aryl hydantoins, comprising
reacting allantoin, hot, in an acid
medium, with an aromatic derivative
which has at least one nuclear proton.**

**The 5-aryl hydantoins produced
thereby are valuable in chemical synth-
esis, in phytopharmacy and in human
therapeutics.**

**Some of the products are claimed
per se.**

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SPECIFICATION

Process for manufacturing racemic 5-aryl hydantoins and novel products thereof

5 The present invention relates to a process for manufacturing racemic 5-aryl hydantoins from allantoin and to the novel products therefrom. 5

5-aryl hydantoins are valuable chemical substances having numerous uses, either in chemical synthesis to obtain certain racemic or split alpha-aminoacids (FR 2 310 986), or in phytopharmacy to counter certain growth disorders of vegetables (US 2 891 069), or lastly in human or animal therapeutics (L.M. Werbel et al., 10 J. Med. Chem.) 20, 1569-72 (1977).

According to the prior art, it is possible to obtain racemic 5-aryl hydantoins, either by cyclisation of arylmalonamides according to C.K. Ingold et al, J. Chem. Soc., 121, 1190 (1922), or of arylcyanacetamides according to T.J. Thompson et al., J. Amer. Chem. Soc., 47, 875 (1925), or of racemic 2-aryl hydantoic acids derived from the action of an alkali cyanate or of urea on racemic alpha-arylglycines according to E.C.

15 Wagner et al., J. Chem. Educ. 73, 266 (1936) or of alpha-aryl alpha-ureidoacetonitrils according to S.L. Ruskin et al., J. Amer. Chem. Soc., 60, 1471 (1938), or by the action of urea on an arylglyoxal according to M.J. Fisher et al., J. Amer. Chem. Soc., 64, 1434 (1934) (1942), or by the action of an alkali cyanide in the presence of ammonium carbonate on benzaldehydes by the method of Berge-Bucherer or on their bisulfite compounds according to J.Klosa, Arch. Pharm., 285, 278 (1952) or on their cyanhydrin according to GB 936 664, or by 20 alkylation of an aromatic by a racemic 5-alkoxy hydantoin according to D. Ben Ishai et al., Tetrahedron 1970, 1289-83.

Certain particular methods are described for preparing racemic 5-parahydroxyphenyl hydantoin, either by reaction of urea on racemic parahydroxymandelic acid according to French patent application 78/22 989, or by the action of urea and of glyoxylic acid on phenol according to BE 865 027.

25 These methods require either the handling of alkali cyanide or the availability of starting materials which are difficult to obtain, such as certain substituted benzaldehydes or 5-alkoxy hydantoins, constituting troublesome drawbacks for industrial manufacture. 25

Now, Applicant has fortuitously discovered that allantoin (racemic 5-ureido hydantoin), in an acid medium, reacts with various aromatic structures to provide racemic 5-aryl hydantoins. The substitution in an acid medium of the ureido group of allantoin by an aromatic group is unexpected and has never been 30 indicated in the chemical literature according to Applicant's knowledge. This arylation of the 2,4-dioxo imidazolidine nucleus is all the more surprising since it is well known that allantoin is stable in an acid medium, since it can be obtained in this medium according to DE AS 1 939 924. 30

In addition, the invention enables novel hydantoins to be obtained which have never been described in the 35 literature to Applicant's knowledge. 35

According to the process of the invention, allantoin is reacted hot, in an acid medium with an aromatic derivative possessing at least one nuclear proton, whether or not in excess, in the presence if necessary of an organic solvent. This reaction generally carried out in concentrated inorganic solvent. This reaction generally carried out in concentrated inorganic acids such as concentrated hydrochloric acid, sulfuric acid, 40 Nordhausen acid (fuming sulfuric acid) is general both with aromatic structures sensitive to electrophilic attack and with aromatic structures deactivated by electro-acceptor groups. If necessary, more particularly when the aromatic derivative used is a high melting solid, it is preferred to carry out this condensation in a conventional organic solvent such as C1 to C4 alcohols or acetic acid. According to the process of the invention, the aromatic derivative may be phenol, alkylphenols such as cresols; diphenols such as 45 resorcinol, pyrocatechol, hydroquinone; triphenols such as pyrogallol as well as the ethers such as anisole, guaiacol, metamethoxyphenol, hydroquinone monomethylether; halogenated phenols such as parachlorophenol, 2,3-dichloro phenol, 2,5-dichlorophenol, 2,4-dichlorophenol, 3,5-dichlorophenol, nitrophenols; aromatics such as benzene, thiophene or their alkylated derivatives such as, for example, toluene, xylenes, mesitylene; benzoic acids such as for example, gallic acid, syringic acid, 3,4,5-trimethoxy benzoic acid; 50 halogenated aromatics such as chlorobenzene, dichlorobenzenes, acetanilide and the like. 50

More precisely, the process of the invention consists of condensing allantoin, hot, between 50°C and 100°C, for 6 to 48 hours, with an excess of aromatic derivative possessing at least one nuclear proton in the presence of a concentrated aqueous solution of strong inorganic acid selected from among concentrated hydrochloric acid $d = 1.18$; sulfuric acid $d = 1.83$; Nordhausen acid or fuming sulfuric acid $d = 1.88$ and, if 55 necessary, in the presence of an organic solvent such as acetic acid or isopropanol, then at the end of the reaction isolating the desired product by methods known in themselves, or by concentration under vacuum of the reaction medium and taking up again with water when working in concentrated hydrochloric acid, or by taking up again of the reaction medium with iced water keeping the pH toward 4 ± 0.5 by the simultaneous addition of caustic soda when working in the presence of sulfuric acid, then of filtering the 60 desired product when it crystallises directly in water or extracting it with a water-immiscible organic solvent and finally, purifying it for recrystallisation in a suitable solvent. 60

The following Examples are given purely by way of illustration and are not to be regarded as limiting the invention.

Example 1

0.5 mole (79 g) of allantoin and 1 mole (124 g) of gualacol are heated for 18 hours at 80°C, in 50 g of isopropanol and 400 g of concentrated hydrochloric acid $d = 1.18$. Then the reaction medium concentrated under vacuum was taken up in 100 cm³ water. In this way 55 g of racemic 5-(4-hydroxy 3-methoxy phenyl) hydantoin was isolated having, after recrystallisation in three volumes of water, a melting point of 200°C (M.P. literature 276°C with decomposition, H.R. Henze et al., J. Amer. Chem. Soc., 64, 522-3 (1942)).

Micro-analysis $C_{10}H_{10}N_2O_4$

M.W. = 222.20

Water determination by the method of K. Fischer 0.8 %

10		C, %	H, %	N, %	10
	calculated with 0.8 % of water	53.61	4.59	12.51	
	found	53.3	4.6	12.5	
15					15

Example 2

Procedure was as in Example 1 but the guaiacol was replaced by 1 mole of phenol. In this way after recrystallisation in water racemic 5-parahydroxyphenyl hydantoin was obtained possessing a melting point of $265 \pm 3^\circ\text{C}$ with a yield of 70 % of the theory calculated with respect to the allantoin utilised (M.P. literature 269-270°C, E.K. Harvil et al., J. Org. Chem., 9, 21-30 (1944)).

Micro-analysis $C_9H_8N_2O_3$

M.W. = 192.17

25		C, %	H, %	N, %	25
	calculated	56.25	4.19	14.58	
	found	56.15	4.30	14.40	

Example 3

Procedure was as in Example 1 but the guaiacol was replaced by 1 mole of paracresol. In this way there was obtained, after recrystallisation in a 9-1 (v/v) water-isopropanol mixture, racemic 5-(2-hydroxy 5-methyl phenyl) hydantoin having a melting point of $258 \pm 3^\circ\text{C}$ with a yield of 70 % of the theory calculated with respect to the allantoin used. To Applicant's knowledge, this product is not described in the literature.

Micro-analysis $C_{10}H_{10}N_2O_3$

M.W. = 206.20

40		C, %	H, %	N, %	40
	calculated	58.24	4.89	13.59	
	found	58.3	4.9	13.5	

Example 4

Procedure was as in Example 1 but the guaiacol was replaced by 1 mole of metacresol. In this way there was obtained, after recrystallisation in a 9-1 (v/v) water-acetone mixture, racemic 5-(2-hydroxy 4-methyl phenyl) hydantoin having a melting point of $244 \pm 3^\circ\text{C}$ with a yield of 75 % of the theory calculated with respect to the allantoin used. To Applicant's knowledge, this product is not described in the literature.

Micro-analysis $C_{10}H_{10}N_2O_3$

M.W. = 206.20

50		C, %	H, %	N, %	50
	calculated	58.24	4.89	13.59	
	found	57.8	5.0	13.45	
55					55

Example 5

Procedure was as in Example 1, but the guaiacol was replaced by 1 mole of orthocresol. In this way, there was obtained, after recrystallisation in a 1-4 (v/v) water-isopropanol mixture, racemic 5-(4-hydroxy 3-methyl phenyl) hydantoin having a melting point of 242°C with a yield of 90 % of the theory calculated with respect to the allantoin used. To Applicant's knowledge, this product is not described in the literature.

Micro-analysis $C_{10}H_{10}N_2O_3$

M.W. = 206.20

	C, %	H, %	N, %
calculated	58.24	4.89	13.59
found	57.9	5.2	13.0

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Example 6

Procedure was as in Example 1, but the guaiacol was replaced by 1 mole of hydroquinone. In this way there was obtained, after recrystallisation in a 1-1 (v/v) acetone-water mixture, racemic 5-(2,5-dihydroxy phenyl) hydantoin decomposing at 170°C with a yield of 90 % of the theory calculated with respect to the allantoin used. To Applicants's knowledge, this product is not described in the literature.

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Micro-analysis $C_9H_8N_2O_4 \cdot H_2O$

M.W. = 226.19

15

	C, %	H, %	N, %	H ₂ O, % *
calculated	47.78	4.45	12.38	7.96
found	47.8	4.3	12.3	8.4

15

20 * determined by the method of K. Fischer.

20

Example 7

Procedure was as in Example 1, but the guaiacol was replaced by 1 mole of resorcinol. In this way, there was obtained, after recrystallisation in 1-1 (v/v) acetone-water, racemic 5-(2,4-dihydroxy phenyl) hydantoin having a melting point of about 300°C with a yield of 50 % of the theory calculated with respect to the allantoin used. To Applicant's knowledge, this product is not described in the literature.

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Example 8

Procedure was as in Example 1, but the guaiacol was replaced by pyrocatechol. In this way, there was obtained, after recrystallisation in water, racemic 5-(3,4-dihydroxy phenyl) hydantoin having a melting point of 240°C $\pm$ 1°C with a yield of 70 % of the theory calculated with respect to the allantoin used (M.P. literature 231-232°C, R. Kuhn et al., *Annalen* 662, 67-71 (1963)).

30

30

Micro-analysis $C_9H_8N_2O_4$

M.W. = 208.18

35

	C, %	N, %	N, %
calculated	51.92	3.88	13.46
found	52.0	4.0	13.4

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Example 9

Procedure was as in Example 1, but the guaiacol was replaced by 1 mole of 2,6-dimethyl phenol. In this way, there was obtained, after recrystallisation in water, racemic 5-(4-hydroxy 3,5-dimethyl phenyl) hydantoin having a melting point of 248 $\pm$ 1°C with a yield of 90 % of the theory calculated with respect to the allantoin used. To Applicants's knowledge, this product is not described in the literature.

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Micro-analysis $C_{11}H_{12}N_2O_3$

M.S. = 220.23

50

	C, %	H, %	N, %
calculated	59.99	5.49	12.72
found	59.9	5.4	12.5

50

55

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Example 10

Procedure was as in Example 1, but the guaiacol was replaced by 1 mole of hydroquinone monomethylether. In this way, there was obtained, after recrystallisation in a 1-1 (v v) water-dimethylformamide mixture, racemic 5-(2-hydroxy 5-methoxy-phenyl) hydantoin decomposing towards 250°C with a yield of 50 % of the theory calculated with respect to the allantoin used, To Applicant's knowledge, this product is not described in the literature.

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60

Micro-analysis $C_{10}H_{10}N_2O_4$

M.W. = 222.20

		C, %	H, %	N, %	
	calculated	54.05	4.54	12.61	
	found	53.9	4.6	12.6	

5

5

Example 11

Procedure was as in Example 1, but the guaiacol was replaced by 1 mole of pyrogallol. In this way, there was obtained, after recrystallisation in 1-1 (v/v) ethanol-water mixture, racemic 5-(2,3,4-trihydroxy phenyl) handantoin having a melting point of $300 \pm 3^\circ\text{C}$ with a yield of 50 % of the theory calculated with respect to the allantoin used. To Applicant's knowledge, this product is not described in the literature.

10 Micro-analysis $\text{C}_9\text{H}_8\text{N}_2\text{O}_5$

10

M.W. = 224.18

		C, %	H, %	N, %	
	calculated	48.22	3.6	12.5	
	found	48.0	4.1	11.6	

20

20

Example 12

Procedure was as in Example 1, but the guaiacol was replaced by 1 mole of 2,6-dimethoxy phenol. In this way, there was obtained after recrystallisation in water, racemic 5-(4-hydroxy 3,5-dimethoxy phenyl) hydantoin having a melting point close to 265°C with a yield of 40 % of the theory calculated with respect to the allantoin used (M.P. Literature 261°C , G. Schmidt et al., *Annalen* 1976, 126-39).

25 Micro-analysis $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_5$

25

M.W. = 252.23

		C, %	H, %	N, %	
	calculated	52.38	4.8	11.11	
	found	52.2	4.9	11.1	

35 *Example 13*

35

Procedure was as in Example 1, but the guaiacol was replaced by 1 mole of orthochlorophenol. In this way, there was obtained, after recrystallisation in a 1-2 (v/v) ethanol-water mixture, racemic 5-(3-chloro 4-hydroxy phenyl) hydantoin having a melting point of $222 \pm 3^\circ\text{C}$ with a yield of 80 % of the theory calculated with respect to the allantoin used. (M.P. literature $240-242^\circ\text{C}$, B. Bognar et al., *Antibiotiki*, 9, 875-80 (1964)).

40 Micro-analysis $\text{C}_9\text{H}_7\text{ClN}_2\text{O}_3$

40

M.W. = 226.63

		C, %	H, %	Cl, %	N, %	
	calculated	47.70	3.11	15.65	12.36	
	found	47.8	3.1	15.5	12.25	

50 *Example 14*

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Procedure was as in Example 1, but the guaiacol was replaced by 1 mole of 2,6-dichlorophenol. In this way, there was obtained, after recrystallisation in a 1-2 (v/v) ethanol-water mixture, racemic 5-(3,5-dichloro 4-hydroxy phenyl) hydantoin having a melting point in the vicinity of 264°C with a yield of 50 % of the theory calculated with respect to the allantoin used. To Applicant's knowledge, this product is not described in the literature.

55 Micro-analysis $\text{C}_9\text{H}_6\text{Cl}_2\text{N}_2\text{O}_3$

55

M.W. = 261.07

		C, %	H, %	Cl, %	H, %	
	calculated	41.4	2.32	27.16	10.73	
	found	41.4	2.5	27.05	10.8	

60 *Example 15*

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Procedure was as in Example 1, but the guaiacol was replaced by 1 mole of beta-naphthol. In this way,

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there was obtained, after recrystallisation in a 1-2 (v/v) ethanol-water mixture, racemic 5-(2-hydroxy 1-naphthyl) hydantoin having a melting point (with decomposition) towards 300°C with a yield of 60 % of the theory calculated with respect to the allantoin used. To Applicant's knowledge, this product is not known in the literature.

5 Micro-analysis $C_{13}H_{10}N_2O_3$
M.W. = 242.23

		C, %	H, %	N, %
10	calculated	64.45	4.16	11.57
	found	64.5	4.3	11.5

Physical analysis NMR of the proton at 60 MHz in deuterated DMSO

15	5.9 ppm	1H	singlet	CH
	7.6	6H	multiplet	aromatic
	10.3	1H	singlet	OH
	8.0-10.8 ppm	2H	multiplet	NH

20 *Example 16*

Procedure was as in Example 1, but the gualacol was replaced by 1 mole of anisole. In this way, there was obtained, after recrystallisation in a 9-1 (v/v) water-methanol mixture, racemic 5-paramethoxyphenyl hydantoin having a melting point of 196°C with a yield of 50 % of the theory calculated with respect to the allantoin used. (M.P. literature 195°C, E.K. Harvill et al., J. Org. Chem., 9, 21-30 (1944)).

25 Micro-analysis $C_{10}H_{10}N_2O_3$
M.W. = 206.20

		C, %	H, %	N, %
30	calculated	58.20	4.89	13.59
	found	58.3	5.0	13.6

35 *Example 17*

0.5 mole (79 g) of allantoin, 200 g of thiophene were heated for 14 hours at 80°C in 50 g of acetic acid and 200 g of concentrated sulfuric acid $d = 1.83$. At the end of the reaction, the reaction medium was poured on to 500 g of crushed ice keeping the pH towards 4 ± 0.5 by the simultaneous addition of caustic soda and then the suspension obtained was extracted with ethyl acetate. The organic extraction phases were then washed with water, and then the solvent removed under vacuum. The residue obtained was recrystallised in 1,2-dichloro ethane. In this way, racemic 5-(2-thienyl)hydantoin was isolated having a melting point of 78-80°C with a yield of 70 % of the theory calculated with respect to the allantoin used (product described : U.S. 3 198 804).

40 Micro-analysis $C_7H_6N_2O_2S \cdot H_2O$
45 M.W. = 200.21

		C, %	H, %	H, %	S, %	H ₂ O, % *
50	calculated	41.99	4.03	14.00	16.01	9.00
	found	42.0	3.95	13.95	16.1	8.9

* determined by the method of K.Fischer.

Example 18

55 Procedure was as in Example 17, but the thiophene was replaced by 200 g of parachlorophenol. In this way, there was obtained, after recrystallisation in a 2-1 (v/v) ethanol-water mixture, racemic 5-(6-chloro 2-hydroxy phenyl) hydantoin having a melting point of 280°C with decomposition with a yield of 60 % of the theory calculated with respect to the allantoin used (M.P. literature 255-257°C, U.S. 3 410 865).

60 Micro-analysis $C_9H_7ClN_2O_3$
M.W. = 226.63

		C, %	H, %	Cl, %	N, %
65	calculated	47.7	3.11	15.65	12.36
	found	47.9	3.2	15.7	12.3

Example 19

Procedure was according to that of Example 17, but the thiophene was replaced by 200 g of 2,4-dichloro phenol. In this way, there was obtained, after recrystallisation in a 4-1 (v/v) ethanol-water mixture, racemic 5-(3,5-dichloro 2-hydroxy phenyl) hydantoin having a melting point of $300 > 5^{\circ}\text{C}$ with decomposition with a yield of 80% of the theory calculated with respect to the allantoin used. To Applicant's knowledge, this product is not described in the literature.

Micro-analysis $\text{C}_9\text{H}_6\text{Cl}_2\text{N}_2\text{O}_3$

M.W. = 261.07

	C, %	H, %	Cl, %	N, %
calculated	41.40	2.32	27.16	10.73
found	41.4	2.35	26.9	10.7

Example 20

Procedure was as in Example 17, but the thiophene was replaced by 200 g of 3,5-dichloro phenol. In this way, there was obtained, after recrystallisation in a 2-1 (v/v) acetone-water mixture, 5-(2,6-dichloro 4-hydroxy phenyl) hydantoin having a melting point with decomposition towards 300°C with a yield of 60 % of the theory calculated with respect to the allantoin used. To Applicant's knowledge, this product is not described in the literature.

Example 21

Procedure was as in Example 17, but the thiophene was replaced by 200 g of 2,3-dichloro phenol. In this way, there is obtained, after recrystallisation in a 1-1 (v/v) ethanol-water mixture, 5-(3,4-dichloro 2-hydroxy phenyl) hydantoin having a melting point with decomposition towards 260°C with a yield of 70 % of the theory calculated with respect to the allantoin used. To applicant's knowledge, this product is not described in the literature.

Micro-analysis $\text{C}_9\text{H}_6\text{Cl}_2\text{N}_2\text{O}_3$

M.W. = 261.07

	C, %	H, %	Cl, %	N, %
calculated	41.40	2.32	27.16	10.73
found	40.9	2.5	26.4	10.7

Example 22

Procedure was according to that of Example 17, but the thiophene was replaced by 200 g of benzene. In this way there was obtained, after recrystallisation in water containing 10 % of isopropanol, racemic 5-phenyl hydantoin having a melting point of $170 \pm 1^{\circ}\text{C}$ with a yield of 88 % of the theory calculated with respect to the allantoin used (M.P. literature $179-180^{\circ}\text{C}$, D. Ben Ishai, Chem. Comm., 1969, 376).

Micro-analysis $\text{C}_9\text{H}_8\text{N}_2\text{O}_2$

M.W. = 176.18

	C, %	H, %	N, %
calculated	61.35	4.58	15.90
found	61.5	4.7	15.9

Example 23

Procedure was according to that of Example 17, but the thiophene was replaced by 200 g of 2,5-dichloro phenol. In this way, there was obtained, after recrystallisation in a 1-2 (v/v) dimethylformamide-water mixture, racemic 5-(2,5-dichloro 4-hydroxy phenyl) hydantoin having a melting point with decomposition towards 270°C with a yield of 80 % of the theory calculated with respect to the allantoin used. To Applicants's knowledge, this product is not described in the literature.

Micro-analysis $\text{C}_9\text{H}_6\text{Cl}_2\text{N}_2\text{O}_3$.

M.W. = 261.07

	C, %	H, %	Cl, %	N, %
calculated	41.40	2.32	27.16	10.73
found	41.0	2.6	26.8	10.5

Example 24

Procedure was according to that of Example 17, but the thiophene was replaced by 200 g of toluene. In this way there was obtained, after recrystallisation in a 1-1 (v/v) acetone-water mixture, racemic 5-paratolyl hydantoin having a melting point of 180°C (capillary tube) with a yield of 80 % of the theory calculated with respect to the allantoin used (M.P. literature 155°C, F.P. Doyle, J. Chem. Soc., 1962, 1440).

5 Micro-analysis $C_{10}H_{10}N_2O_2$
M.W. = 190.20

		C, %	H, %	N, %	
10	calculated	63.15	5.30	14.73	10
	found	62.7	5.4	14.6	

Example 25

15 Procedure was as in Example 17, but the thiophene was replaced by 200 g of mesitylene. In this way there was obtained, after recrystallisation in a 1-2 (v/v) methanol-water mixture, racemic 5-mesityl hydantoin having a melting point of 218°C with a yield of 90 % of the theory calculated with respect to the allantoin used. To Applicant's knowledge, this product is not described in the literature.

20 Micro-analysis $C_{12}H_{14}N_2O_2$
M.W. = 218.25

		C, %	H, %	N, %	
25	calculated	66.04	6.46	12.84	25
	found	65.8	6.6	12.65	

Example 26

30 0.5 mole (79 g) of allantoin and 500 g of chlorobenzene were heated for 48 hours at 70°C in 200 g of concentrated sulfuric acid $d = 1.83$ and 100 g of Nordhausen sulfuric acid $d = 1.88$. Then the reaction mixture was poured on to 500 g of crushed ice keeping the pH towards 4 ± 0.5 by the simultaneous addition of caustic soda. The crystallised product obtained was then drained. After drying to constant weight, under vacuum at 60°C and recrystallisation in a methanol-water mixture, 5-parachlorophenyl hydantoin was obtained having a melting point of 142°C with a yield of 88 % of the theory calculated with respect to the allantoin used (M.P. literature 142-144°C, D. Ben Ishai et al., J. Heterocyclic Chem., 7, 1289-93, (1970)).

35 Micro-analysis $C_9H_7ClN_2O_2$
M.W. = 210.63

		C, %	H, %	Cl, %	N, %	
40	calculated	51.32	3.35	16.84	13.30	40
	found	51.4	3.1	16.9	13.0	

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Example 27

50 Procedure was as in Example 26, but the chloro-benzene was replaced by 500 g of parahydroxybenzoic acid. In this way there was obtained, after recrystallisation in a 2-3 (v/v) acetic acid-water mixture, racemic 4-hydroxy 3-(2,4-dioxo 5-imidazolidinyl) benzoic acid with a yield of 40 % of the theory calculated with respect to the allantoin used. To Applicant's knowledge, this product is not described in the literature.

Micro-analysis $C_{10}H_8N_2O_6$
M.W. = 236.19

		C, %	H, %	N, %	H ₂ O, %*	
55	calculated	50.85	3.42	11.86		55
	found	49.8	3.6	11.4	1.2	
60	calculated in 1.2 % of water	50.24	3.51	11.72	1.2	60

* determined by the method of K. Fischer.

Example 28

Procedure was according to that of Example 26, but the chlorobenzene was replaced by 500 g of acetanilide. In this way there was obtained, after recrystallisation in a 1-1 (v/v) ethanol-water mixture, racemic 5-(4-acetamido phenyl) hydantoin having a melting point higher than 300°C with a yield of 40 % of the theory calculated with respect to the allantoin used (M.P. literature 250°C, R. Kuhn et al., *Annalen*, 662, 67-71 (1963)).

Example 29

Procedure was according to that of Example 27, but the chlorobenzene was replaced by 500 g of parantrophanol. In this way, there was obtained, after recrystallisation in a 2-1 (v/v) dimethylformamide-water mixture, racemic 5-(5-nitro 2-hydroxy phenyl) hydantoin having a melting point with decomposition towards 250°C with a yield of 50 % of the theory calculated with respect to the allantoin used. To Applicant's knowledge, this product is not described in the literature.

Examples 30, 31 and 32

Procedure was according to that of Example 26, but the chlorobenzene was replaced by 500 g of 3,4,5-trimethoxy benzoic acid. In this way there was obtained, after recrystallisation in a 10-1 (v/v) methanol-water mixture, racemic 2-(2,4-dioxo 5-imidazolidinyl) 3,4,5-trimethoxy benzoic acid having a melting point of 230 ± 3°C with decomposition with a yield of 90 % of the theory calculated with respect to the allantoin used. To Applicant's knowledge, this product is not described in the literature.

Micro-analysis $C_{13}H_{14}N_2O_7$
M.W. = 310.26

		C, %	H, %	N, %	
25	calculated	50.32	4.55	9.03	25
	found	50.3	4.5	9.1	

In the same way, using syringic acid, there was obtained with a yield of 71 %, racemic 2-(2,4-dioxo 5-imidazolidinyl) 3,5-dimethoxy 4-hydroxy benzoic acid having a melting point with decomposition towards 250°C after recrystallisation in a 1-1 (v/v) dimethylformamide-acetic acid mixture.

In the same way using gallic acid, there was obtained with a yield of 70%, racemic 2-(2,4-dioxo 5-imidazolidinyl) 3,4,5-trihydroxy benzoic acid having an indistinct melting point towards 250°C after recrystallisation in water.

To Applicant's knowledge, these products are not described in the literature.

CLAIMS

1. Process for manufacturing racemic 5-aryl hydantoins, comprising reacting allantoin, hot, in an acid medium, with an aromatic derivative which has at least one nuclear proton.
2. Process according to Claim 1, wherein the allantoin is reacted in a strong inorganic acid in aqueous solution, optionally in the presence of an organic solvent.
3. Process according to Claim 2, wherein the strong inorganic acid is selected from concentrated hydrochloric acid, concentrated sulfuric acid, Nordhausen fuming sulfuric acid, or is a mixture of these acids.
4. Process according to Claim 2 or 3, wherein the organic solvent is selected from acetic acid and C_{1-4} aliphatic alcohols.
5. Process according to Claim 2, 3 or 4, wherein the reaction is carried out at a temperature of 50°C or higher.
6. Process according to any one of the preceding claims, wherein the aromatic derivative is selected from the following compounds: phenol, alkylphenols comprising cresols; diphenols comprising resorcinol, pyrocatechol, hydroquinone; triphenols comprising pyrogallol, as well as the ethers comprising anisole, guaiacol, metamethoxyl-phenol, hydroquinone monomethylether; halogenated phenols comprising para-chlorophenol, 2,3-dichloro phenol, 2,5-dichloro phenol, 2,4-dichloro phenol, 3,5-dichloro phenol, nitrophenols; the aromatics comprising benzene, thiophene and their alkylated derivatives comprising toluene, xylenes, mesitylene; benzoic acids comprising gallic acid, syringic acid, 3,4,5-trimethoxy benzoic acid; and halogenated aromatics comprising chlorobenzene, dichlorobenzenes, acetanilide.
7. Process according to Claim 1, substantially as hereinbefore described in any one of Examples 1 to 32.
8. A racemic 5-aryl hydantoin when obtained by a process as claimed in any one of the preceding claims.
9. 5-(2-hydroxy 5-methyl phenyl) hydantoin.
10. 5-(2-hydroxy 4-methyl phenyl) hydantoin.
11. 5-(2,5-dihydroxy phenyl) hydantoin.
12. 5-(2,4-dihydroxy phenyl) hydantoin.
13. 5-(2-hydroxy 5-methoxy phenyl) hydantoin.
14. 5-(2,3,4-trihydroxy phenyl) hydantoin.
15. 5-(3,5-dichloro 4-hydroxy phenyl) hydantoin.

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| | 16. | 5-(2-hydroxy 1-naphthyl) hydantoin. | |
| | 17. | 5-(3,5-dichloro 2-hydroxy phenyl) hydantoin. | |
| | 18. | 5-(2,6-dichloro 4-hydroxy phenyl) hydantoin. | |
| | 19. | 5-(3,4-dichloro 2-hydroxy phenyl) hydantoin. | |
| 5 | 20. | 5-(2,5-dichloro 4-hydroxy phenyl) hydantoin. | |
| | 21. | 5-mesityl hydantoin. | 5 |
| | 22. | 4-hydroxy 3-(2,4-dioxo 5-imidazolidinyl)benzoic acid. | |
| | 23. | 5-(5-nitro 2-hydroxy phenyl) hydantoin. | |
| | 24. | 2-(2,4-dioxo 5-imidazolidinyl) 3,4,5-trimethoxy benzoic acid. | |
| 10 | 25. | 2-(2,4-dioxo 5-imidazolidinyl) 3,5-dimethoxy 4-hydroxy benzoic acid. | |
| | 26. | 2-(2,4-dioxo 5-imidazolidinyl) 3,4,5-trihydroxy benzoic acid. | 10 |
| | 27. | 5-(4-hydroxy-3,5-dimethyl phenyl) hydantoin. | |

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